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Severe somatization in women is associated with altered cerebral glucose metabolism

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ABSTRACT

Background. Somatization is a clinical phenomenon characterized by multiple, medically unexplained somatic symptoms. The pathophysiology remains unknown. We aimed to test the hypothesis of a central nervous system dysfunction in the pathophysiology of this disorder.

Method. We studied 10 female patients diagnosed as having somatization disorder or undifferentiated somatoform disorder with no current Axis I disorders according to DSM-IV. They were compared with 17 healthy female volunteers using brain [18F]-fluorodeoxyglucose-PET with MRI reference.

Results. The patients had lower cerebral metabolism rates of glucose ($P<0{\cdot}05$) in both caudate nuclei, left putamen and right precentral gyrus compared with healthy volunteers.

Conclusions. This is the first study to demonstrate changes in brain metabolism in somatizing women. The regional cerebral hypometabolism is probably associated with the pathophysiology of somatization.

INTRODUCTION

Somatization is considered to be present in patients who have symptoms that suggest physical illness but remain unconfirmed by objective findings. Somatizing patients are usually frequent attenders in health care (Escobar *et al.* 1987; Karlsson *et al.* 1997). These patients are functionally disabled and their health care charges are extraordinarily high (Quill, 1985; Smith *et al.* 1986). Somatizing patients are also often perceived by medical staff to be frustrating (Lin *et al.* 1991). The category of somatoform disorders is reserved for patients of this type. The diagnosis of somatoform illness is based on the exclusion of known physical disorders and some formal criteria based on symptom presentation. The relationship of somatoform disorders to fashionable diagnoses, e.g. chronic fatigue syndrome, fibromyalgia and multiple chemical sensitivity, remains unclear. The pathophysiology of somatization is largely unknown and it has usually been considered a 'psychogenic' state, because no objective findings are associated with the disorder.

METHOD

Study population

We studied 10 female patients and 17 healthy female volunteers (controls) with PET using 2-[18F]-fluoro-2-deoxy-D-glucose (FDG) as a tracer. All patients met the criteria for somatization disorder ($N=6$) or undifferentiated somatoform disorder ($N=4$) according to the DSM-IV diagnostic classification. The patients were recruited for the study through general practitioners, consultation–liaison psychiatrists

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Table 1. *Characteristics of the patients*

Patient	Age	Diagnosis	Symptoms
1	44	Somatization disorder	Symptoms since adolescence, including e.g. lower abdominal pains, oedema, low back pain, headaches, leukorrhoea, menstrual problems, twitching in the temporal area. Investigated thoroughly, no formal somatic diagnosis
2	45	Undifferentiated somatoform disorder	Symptoms for 6 years, including e.g. headaches, menstrual pains, pain in the left eye, problems with urinary continence, joint pains, nausea, muscle weakness. Diagnosis: fibromyalgia
3	47	Undifferentiated somatoform disorder	Symptoms since childhood, including e.g. stomach pains, vertigo, headaches, palpitations, trembling of hands, problems with vision. Diagnosis: fibromyalgia
4	58	Undifferentiated somatoform disorder	Symptoms for >10 years, including e.g. weakness, chest pains, pains in the eyes, insomnia, stomach pains, vertigo, back pains. No definite somatic diagnosis
5	55	Undifferentiated somatoform disorder	Symptoms for >15 years, including e.g. headaches, fatigue, pains in the eyes, stomach aches, vertigo, cough, diffuse pains, problems with bowel evacuation. Diagnosis: fibromyalgia
6	53	Somatization disorder	Symptoms since the age of 13, including e.g. vertigo, weakness of the hands, stomach pains, menstrual problems, fatigue, tremor, problems with breathing. Diagnosis: lactose intolerance
7	26	Somatization disorder	Symptoms since adolescence, including e.g. vomiting, headaches, problems with vision, low back pains, dyspepsia, menstrual problems. No definite somatic diagnosis
8	49	Somatization disorder	Symptoms since childhood, including e.g. headaches, menstrual problems, stomach pains, vomiting, chest and neck pain, urinary urgency. Somatic diagnosis: allergic rhinitis
9	40	Somatization disorder	Symptoms for at least 12 years, including e.g. problems with vision, headaches, weakness, stomach pains, urinary incontinence, pain during intercourse, severe menstrual pains. No somatic diagnosis
10	49	Somatization disorder	Symptoms for >10 years, including e.g. numbness of the extremities, muscle and joint pains, stomach pains, problems with vision in the right eye, lack of libido, menstrual problems, diarrhoea. Somatic diagnosis: fibromyalgia

and other specialists working in the catchment area of Turku University Central Hospital. Recruiting a patient to the study implied long-lasting vague symptoms and unexplained medical symptoms or a previously established diagnosis of somatization disorder. It should be emphasized that all the patients had been investigated thoroughly in several somatic clinics during the years, but no somatic diagnoses that could account for all their symptoms had been found. The controls were volunteers without any history of illness and their current state of health was good.

To minimize the risk of confusing the findings of somatizing patients with the symptoms of some other psychiatric illness, a thorough investigation was made to exclude all the patients with co-morbid Axis I psychiatric illness. For this purpose the patients also filled in the SCL-90 (Derogatis *et al.* 1973). The patients' characteristics, including a description of some of their symptoms, are shown in Table 1, and the SCL-90 mean scores in Table 2. A few of the controls were drawn from a control pool of the PET Centre. This is why we do not have SCL-90 scores for all the controls. The patients, however, score near the range of a Finnish normal population (Holi *et al.* 1998) in all but one subscale (somatization). However, two patients had relatively high scores in the depression subscale, although in the clinical interviews they were not evaluated as suffering from clinical depression. All but two of the patients and all of the volunteers were right-handed. The mean

Table 2. *SCL-90 scores: patients only*

SCL subscale	Mean	(S.D.)
Somatization	1·4990	(0·8138)
Obsessive–compulsive	1·0200	(0·5731)
Anxiety	0·6200	(0·4442)
Interpersonal sensitivity	0·9570	(0·5588)
Depression	1·0380	(0·7201)
Hostility	0·5840	(0·3793)
Phobic anxiety	0·2700	(0·3261)
Paranoid ideation	0·6850	(0·5963)
Psychoticism	0·4500	(0·4334)

age of the patients was 46·90 years (S.D. = 9·00, range = 26–58) and the mean age of the controls was 49·20 years (S.D. = 6·50, range 39–64) ($P = 0·396$). The venous blood glucose value was 5·55 mmol/l (S.D. = 0·55, range 4·80–6·30) in the patients and 5·47 mmol/l (S.D. = 0·85, range 4·00–7·10) in the volunteers ($P = 0·792$). Neither the mean ages nor the venous blood glucose values of the patients and the controls differed statistically significantly.

Case identification

The potential cases were interviewed by a psychiatric resident, who elicited the basic information about each patient's personal and illness history, symptoms, symptom attribution, social background and relationships as well as the diagnostic procedures made and the treatments that had been given. The patients' medical records were also reviewed if that was considered useful for the diagnostic procedure. We only enrolled patients who were 60 years of age or younger. A diagnosis of somatization disorder or undifferentiated somatoform disorder was set if apparent.

The second phase included an interview with a research psychiatrist, who audited the first phase results and confirmed or rejected the diagnosis of somatization disorder or undifferentiated somatoform disorder. A few patients with co-morbid Axis I disorder were excluded at this phase.

The third phase consisted of validation of the diagnoses. Two psychiatrists independently set diagnoses for the selected patients using the written information collected about the patients and blind to each other's diagnostic classification. Only the patients who received a diagnosis of somatization disorder or undifferentiated somatoform disorder from both investigators were included. Because in the process of diagnosing a somatoform disorder, a clinical evaluation about the nature of the somatic symptoms and significance of the physical findings is essential, we considered that a structured psychiatric interview would not give any additional value in the diagnostic procedure. Instead we thought that two separate clinical evaluations were necessary. To verify the absence of co-morbid axis I disorders, a symptom questionnaire was used.

Study design and analysis

Informed written consent according to the Declaration of Helsinki was obtained from each participant before the study. The investigation had the approval of the ethics committees of Turku University, Turku University Central Hospital and Turku City Hospital.

The subjects selected for the study had taken no psychopharmacological medication, enzyme-inducing agents, caffeine or alcohol or smoked tobacco for at least 7 days prior to the PET study. All subjects fasted for at least 4 h before the PET scan.

On the day of the PET study, an intravenous line was inserted in each forearm, one for blood chemistry assessments (blood glucose at 0, 30 and 50 min and 21 activity samples) and the other for tracer (FDG). A warming cushion was bound around the forearm to ensure proper blood flow during the collection of blood samples. The subject was then positioned in the scanner with three-dimensional laser alignment with reference to the orbitomeatal line parallel to the detector rings.

All the subjects were scanned with the GE Advance tomograph (General Electrics Medical Systems, Milwaukee) at Turku PET Centre. The subjects were awake during the PET scanning, and the study was performed in a dimly lit room with minimal auditory stimulation. The scanning was started at the time of the tracer injection, and it took 50 min of 2D dynamic imaging in ten 5 min frames. The time course of fluorine-18 radioactivity was determined from altogether 21 venous blood samples, (1, 1·5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 15, 20, 25, 30, 35, 40, 45, 50 min after tracer injection), and the blood glucose level was measured at 0, 30 and 50 min.

FDG was synthesized with slight modifications according to the method described by

Hamacher *et al.* (1986). The radiochemical purity exceeded 99%, and the specific radioactivity at the end of the synthesis was >75 GBq/μmol (2 Ci/μmol). The subjects were given 5 ml of the solution with a dose of about 3·7 MBg/kg (0·1 mCi/kg) of [18F]-FDG intravenously in 1 min.

Thirty-five continuous transaxial slices (4·25 mm) were acquired with an 18-ring bismuth germinate whole-body scanner with an axial field of view of 14·8 cm. The resolution was 4·2 mm full width at half maximum (FWHM) in all directions. All data were corrected for dead time, tracer decay and measured photon attenuation and reconstructed with fitted activity curve by patpar in 128 × 128 pixel by pixel matrices.

Magnetic resonance imaging (MRI) was done on all participants as anatomic reference (1.5 Tesla instrument). A reconstructed PET image and MRI were fitted with Amirfit software to get equal slice levels. This program fits the images according to the surface of the brain.

Altogether 30 regions of interest (ROIs), 15 for each hemisphere, were drawn individually at least on four slices in the following transaxial grey matter structures: superior, medial and inferior frontal gyrus, anterior gingulus, pre- and post-central gyrus, temporal gyrus, parietal gyrus, hippocampal area (hippocampus and parahippocampus) and occipital lobe. In addition, ROIs were also drawn in the thalamus, caudate, putamen, cerebellum and cerebrum. The ROIs were identified by visual inspection with reference to the neuroanatomical atlas of Aquilonius & Eckernäs (1980) and to the fitted MRI. The average glucose consumption was computed for each ROI. The left-handed patients were analysed by reversing the left–right axis in the brain. The images were scaled to a global cerebral glucose metabolic rate of μmol/100 g tissue per minute by multiplying with blood glucose. The lumped constant value used was 0·81 (Hasselbach *et al.* 1998). This constant corrects for the difference between glucose and fluorodeoxyglucose. The MRI reference images were viewed by a neuroradiologist blinded to the subject's status (patient/control).

Statistical analysis

The data are presented as means. The continuous variables for glucose metabolism were compared by Student's *t* test. All tests were two-tailed, and a *P* value of 0·05 was considered the level of statistical significance. The SPSS (version 7.5) statistical computer package was used for the computations.

Table 3. *Regional cerebral metabolic rates of glucose (μmol/100 g tissue per minute) in the brains of the patients and controls (areas with significant differences in bold typeface)*

Brain area	Patients	Controls	*t*	df	*P*
R anterior cingulate	24·62	26·44	−1·261	25	0·219
L anterior cingulate	24·90	26·67	−1·164	25	0·256
R caudate nucleus	**27·29**	**30·79**	**−2·145**	**25**	**0·042**
L caudate nucleus	**26·70**	**29·98**	**−2·113**	**25**	**0·045**
R hippocampal area	19·85	21·35	−1·532	25	0·138
L hippocampal area	20·32	21·34	−1·057	25	0·301
R inferior frontal lobe	28·03	30·19	−1·375	25	0·181
L inferior frontal lobe	27·35	30·01	−1·654	25	0·111
R medial frontal lobe	27·55	30·42	−1·717	25	0·098
L medial frontal lobe	27·65	30·26	−1·447	25	0·160
R occipital lobe	26·83	27·33	−0·217	25	0·830
L occipital lobe	26·63	27·02	−0·172	25	0·865
R parietal lobe	25·13	25·28	−0·067	25	0·947
L parietal lobe	25·23	25·18	0·027	25	0·979
R postcentral gyrus	24·86	26·84	−1·342	25	0·192
L postcentral gyrus	24·67	26·73	−1·516	25	0·142
R precentral gyrus	**25·06**	**27·61**	**−2·066**	**25**	**0·049**
L precentral gyrus	25·23	27·58	−1·941	25	0·064
R putamen	28·87	31·60	−1·472	25	0·153
L putamen	**28·01**	**31·71**	**−2·168**	**25**	**0·040**
R reference area*	14·31	14·72	−0·389	25	0·701
L reference area*	14·24	14·70	−0·396	25	0·695
R superior frontal lobe	25·10	27·38	−1·350	25	0·189
L superior frontal lobe	25·09	27·51	−1·467	25	0·155
R thalamus	24·41	25·63	−1·684	25	0·105
L thalamus	24·41	25·76	−1·617	25	0·118
R temporal lobe	26·15	28·85	−0·636	25	0·531
L temporal lobe	26·54	29·24	−0·744	25	0·464

R, Right; L, Left.
* White matter.

RESULTS

Neither age nor venous blood glucose level was statistically significantly different in the patients and the controls. However, we found areas of reduced glucose metabolism in the patients compared to the controls. The metabolic rates as μmol/100 g tissue per minute in the different brain areas are displayed in Table 3.

The regional cerebral metabolic rate of glucose (rCMRGlc) was reduced in the right caudate nucleus ($P=0·042$), left caudate nucleus ($P=0·045$), right precentral gyrus ($P=0·049$) and left putamen ($P=0·040$) (Fig. 1*a–d*). The regional cerebral metabolic rate of glucose

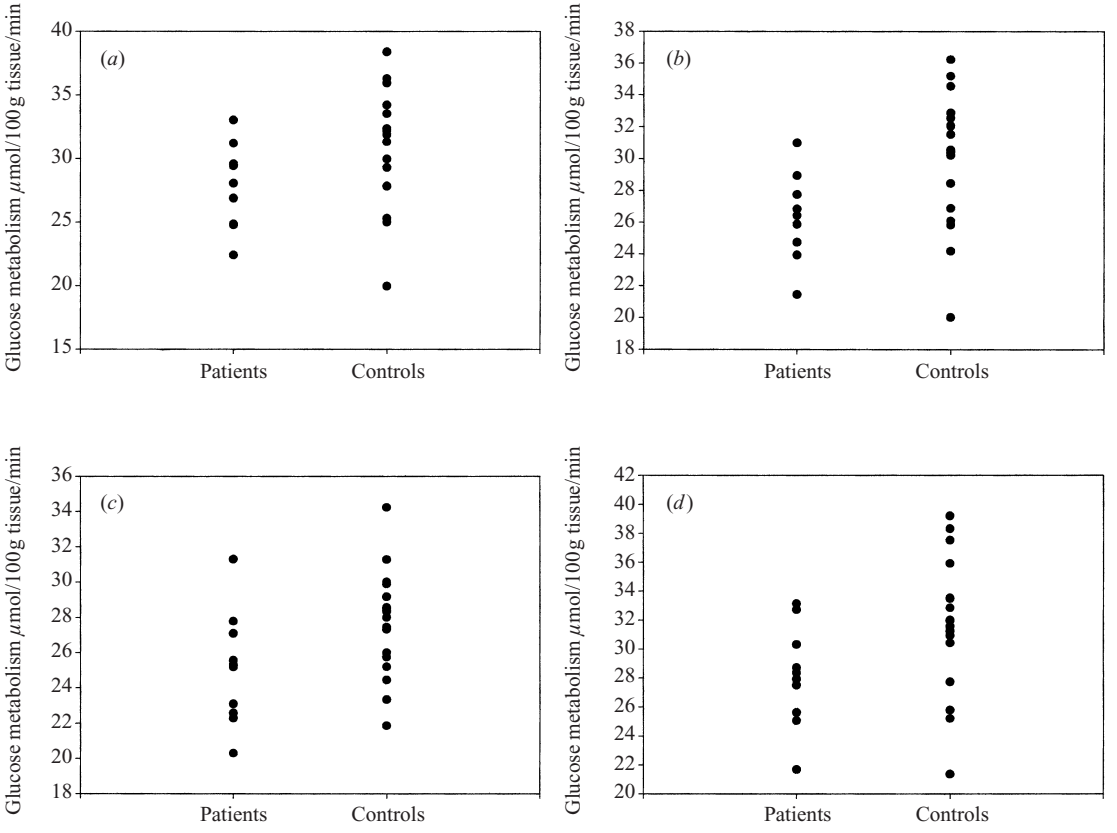

FIG. 1. Regional cerebral glucose metabolism in the brains of individual patients and controls: (*a*) right caudate nucleus; (*b*) left caudate nucleus; (*c*) right precentral gyrus; (*d*) left putamen.

(rCMRGlc) in the cerebellum did not differ between the patients and the healthy volunteers ($P = 0{\cdot}128$). Also, glucose metabolism in the cerebrum did not differ between the patients and the healthy volunteers ($P = 0{\cdot}066$). No left–right asymmetry in the cerebrum and cerebellum or any detectable anatomic changes in the cerebrocerebellar system were seen.

There was also a tendency towards hypometabolism in the left precentral gyrus and in the right medial frontal lobe, but these differences between the patients and the controls did not reach statistical significance. The trend of diffuse hypometabolism may also be seen from comparison of the whole frontal cortex area.

Because two of the patients had a score of 1·92 in the depression subscale of SCL-90, we wanted to look at the possible effects of depressive symptoms to the FDG-findings. We, thus, made a new analysis by excluding these two patients. This made the findings even more prominent. The difference between the patients and the controls in the FDG-values in the areas of hypometabolism became more significant (right nucleus caudatus $P = 0{\cdot}005$, left nucleus caudatus $P = 0{\cdot}016$, right precentral gyrus $P = 0{\cdot}019$, left putamen $P = 0{\cdot}016$), and even new hypometabolic areas emerged (medial prefrontal lobe on both sides, postcentral gyrus on both sides, left precentral gyrus, right putamen, and thalamus on both sides).

DISCUSSION

This is the first study to show that there are changes in brain metabolism in chronically somatizing women. Co-morbid Axis I psychiatric illness was ruled out by a thorough examination of the patients, which means that the results are probably not contaminated by the

effects of other psychiatric illness which could involve similar changes. Quite the contrary, when the two patients with relatively high scores in the depression subscale of the SCL-90 were excluded from the analysis, the findings were even clearer. There were also no focal abnormalities in the MRI scans of the patients that could explain the hypometabolism.

Four of the patients had received a diagnosis of fibromyalgia earlier. When we looked at the symptoms patterns of these patients, it was clear that fibromyalgia did not explain all of these patients symptoms. In Finland the diagnosis of somatization disorder is not well known, and a diagnosis of fibromyalgia is often given in unclear cases. Also the health care system presumes a formal diagnosis for a single patient in order to receive system welfare (e.g. sickleave economic compensation). Additionally, the diagnosis of fibromyalgia is easily accepted by the patients, and is less stigmatizing than psychiatric diagnoses. Also, the relationship of such fashionable diagnoses as fibromyalgia, chronic fatigue syndrome, etc., and somatoform disorders remain unclear. One possibility is that some of these new disease entities actually fall into the category of somatoform illnesses.

It should also be emphasized that all of the patients in our sample had been suffering from their symptoms for years, and all the patients had had several symptoms in different organ systems. In fact, in all patients with a diagnosis of undifferentiated somatoform disorder, only one symptom was lacking or the age of the patient at the beginning of the symptoms was too high, to fulfil all the criteria of somatization disorder (only some examples of the patients symptoms are described in Table 1). It therefore seems that our findings apply to chronically somatizing patients with multiple symptoms, and it may be that some patients who fulfil the criteria of undifferentiated somatoform disorder, but who have had their symptoms for a shorter period or have only one or a few symptoms also differ neurobiologically from our patients.

Our study seems to imply that somatization bears some neurobiological resemblance to depression. Several studies have shown decreased regional brain activity measured by cerebral FDG metabolism or blood flow in depression, especially in the basal ganglia (Baxter *et al.* 1985; Buchsbaum *et al.* 1986) and frontal cortex (Bench *et al.* 1992; Rubin *et al.* 1995). Because our patients were not depressed at the time, the somewhat overlapping findings with depression could be associated with the somatic symptoms that are so common in both illnesses. However, many patients had had episodes of depression earlier, so our findings could also reflect some residual changes of depression. This, however, seems unlikely because usually the metabolic changes in the brain in depression normalize after recovery (Bench *et al.* 1995). Also, although we do not have SCL-90 data on all the controls, this does not decrease the significance of the findings. Namely, if some of the healthy controls had been depressed, which is most unlikely, this could have reduced the difference between the controls and the patients.

There is a big gap in our knowledge about the neurobiology of somatization. According to Bell (1994), we have failed to consider the possibility that some cases of somatization disorder may have non-psychogenic, possibly even directly organic, aetiologies by labelling them as 'psychogenic' states. She hypothesizes that somatization (like other psychiatric disorders) could possibly have a neurobiological basis in kindling-like phenomena.

Although it is too early to understand clearly the mechanisms involved in somatization, we conclude that the regional cerebral hypometabolism pointed out with FDG would be associated with the pathophysiology of somatization, and thus, linked with the multiple symptoms seen in this disorder. The results of our study are another finding that suggests a categorical distinction between physical and psychological illness may be arbitrary. Because of the explorative nature of the study, we decided to perform a two-tailed t test without correction for multiple comparisons (Bonferroni) in the statistical analyses. As the number of comparisons increases above eight to 10 the probability required to conclude that a real difference exists becomes much larger than it really needs to be and the method becomes overconservative. In a first study with a limited amount of studied patients, with small real life differences in the regional metabolic rates between different conditions, and very limited information of the neurobiology of somatization, this should be accepted. This, however, makes it possible that some of the

findings are due to chance. Because of the probably heterogenic nature of this illness and the small number of subjects in this study, these results should be replicated before any final conclusions can be made.

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